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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/802,518	03/09/2001	Gary Van Nest	377882001100	9215

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EXAMINER
PAPPU, SITA S

ART UNIT	PAPER NUMBER
1636	7

DATE MAILED: 04/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/802,518	Applicant(s) VAN NEST, GARY	
	Examiner Sita Pappu	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) 1-35 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-35 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-35 are pending in the instant application. This paper contains an examination of the claims 1-35 on their merits. Preliminary amendment filed in paper #5 on 07/30/2001 and IDS filed in paper # 6 on 01/03/2002 have been entered.

Priority

Applicant's claim to a benefit of provisional application 60/188,556 filed on 03/10/2000 is acknowledged.

Drawings

The drafts person objected to the drawings. See attached PTO-948. The drawings are acceptable for examination purposes only.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 29-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the

enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

Nature of the Invention:

The nature of the invention of claims 1-9 is drawn to a method for preventing a symptom of herpes simplex virus infection in an individual who has been exposed to herpes simplex virus, comprising administering a composition of claims 29-35, comprising a polynucleotide comprising an immunostimulatory sequence to said individual and is directed to gene therapy with immunostimulatory polynucleotides.

Breadth of claims:

The claims 1-9 encompass the use of the said method in preventing a symptom of herpes simplex virus infection in any individual and any mammal and thus have a very broad scope. The kits and compositions of claims 29-35 are directed to preventing the said viral infection and are not enabled for the intended use and thus have a very broad scope.

Amount of guidance in the specification and working examples:

The specification discloses the use of an immunostimulatory sequence (ISS) to treat and/or reduce the severity of symptoms and/or increase the recovery time of

herpes simplex virus exposed mice and guinea pigs. The specification does not disclose the use of the said ISS in preventing the symptoms of a human or animal herpes simplex virus infection. The disclosed use is limited to reducing the severity of, and not preventing, a symptom of herpes simplex virus infection in mice and guinea pigs. The specification teaches that the administration of ISS DNA sequences induces an immune response with a Th1–type bias as indicated by secretion of Th1-associated cytokines (specification, page 5, line 7) and that preventing a symptom of infection by herpes virus (page 16, line 20) means that the symptom does not appear after exposure to the virus. The examples provided teach that the administration of the ISS sequences to mice exposed to herpes simplex virus 2 leads to improved survival as compared to animals that received non-ISS sequences, PBS or no treatment (Fig.1) and to less cumulative mean herpetic lesions in ISS treated guinea pigs that have previously been infected with HSV-2 (Figs. 2 and 3) and that the magnitude of genomic equivalents per shedding from the herpetic lesions is less in guinea pigs (Fig. 4). Other than this, the specification does not teach how the administration of the ISS sequences leads to the prevention of symptom development since it has not been shown in mice and guinea pigs that were used as the models in the instant application. It is unpredictable, in such a situation how these results in the animal models would translate into symptom prevention in the model animals used in the instant invention and much less in any mammal and any individual.

State of the art, predictability, amount of experimentation necessary and skill level of the artisan:

At the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2).

Further, Mountain (2000; TIBTECH vol.18, pp119-128) states that the delivery of naked DNA results in lower delivery efficiency than vectors, brief expression in most tissues and unsuitability for targeting and that it is a disadvantage for chronic-disease therapy (see page 124, left column, paragraph 2). Romano (2000; Stem Cells vol. 18, pp19-39) concurs and states that these limitations "make difficult the in vivo applications of nonviral gene delivery systems" (see page 30, right column, paragraph2, lines 3-6).

Krieg, A. M. (1999; J. Gene Med. Vol 1, pp 56-63) states that optimal ratio of CpG stimulatory motifs to CpG neutralizing motifs should be maintained in order to achieve an optimal immune response. Krieg further suggests that the immunostimulatory effect of the CpG nucleotides is achieved as a result of the unmethylated state of the immunostimulatory CpG motifs, and that it may have an unwanted effect of acute inflammatory response which could be exacerabated if the DNA uptake is enhanced by co-administration of lipids, as exemplified by studies in mice and cystic fibrosis patients, and further suggests that the generation of immune responses is to be avoided in any gene therapy application (page 59, right column, paragraph 3) considering the inflammatory reactions. Tokunaga (1999) concurs and states that the ISS DNA may play an important pathogenic role in the inflammatory lung disease (page 8, left column, sub-section vi, paragraph 2).

Tokunaga et al (1999; Jpn. J. Infect. Dis. 52:1-11) further state that the activation of the immune system with ISS DNA could cause both beneficial as well as deleterious consequences (page8, left column, sub-section vi, paragraph 1) which is exemplified by the development of systemic lupus erythematosis (SLE) that was attributed to the ISS in bacterial DNA as a cause of over-expression of immune cytokines such as IL-6, and resistance to apoptosis, which there-by potentially allowed the survival of autoreactive cells (page 8, right column, paragraph 2).

Thus, the specification is not enabling for claims 1-9 and 29-35 due to the insufficient guidance provided and further, due to the unpredictability of gene therapy (as explained herein below), would have required a skilled artisan to engage in undue

experimentation to practice the invention to prevent the symptom of herpes simplex virus infection.

Claims 10-19, 20-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing severity and/or recurrence of a symptom of herpes simplex virus 2 infection in mice and guinea pigs infected with herpes simplex virus, by administering a polynucleotide comprising an immunostimulatory sequence to said mice and guinea pigs at a dose sufficient to reduce the severity and/or recurrence of a symptom of HSV-2 infection, wherein the ISS comprises the sequence set forth in SeqID NO:1 or 9, does not reasonably provide enablement for a method of reducing the severity of a symptom of HSV-2 infection in any individual or mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The nature of the invention of claims 10-28 is directed to gene therapy with ISS sequences to reduce the severity and/or recurrence of HSV-2 infection.

Claims 10-28 are drawn to a method of reducing severity and/or recurrence of a symptom of HSV-2 infection in any individual infected with herpes simplex virus, comprising administering a composition comprising a polynucleotide comprising an immunostimulatory sequence to said individual and have a very broad scope.

The specification is not enabling for a method of reducing the severity and/or recurrence of a symptom of HSV-2 infection in any individual or mammal exposed to

HSV-2. The amount of guidance in the specification and working examples are limited to the applicability of the claims to a method of reducing the severity and/or recurrence of infection in mice and guinea pigs (examples 1 and 2, pages 42-47). The working examples teach that the disease development is delayed in mice administered with the ISS of the instant case (example 1, page 42) and that lesion development is reduced in guinea pigs (example 2, page 44).

Claims 10-28 are drawn to a mammal, which includes humans. In many cases, studies in other animal systems do not reflect and/or predict success in human system. The specification enables only a limited scope of the claimed method in only mice and guinea pigs and does not predict success in humans. To put it in the words of Kmiec (1999; American Scientist, vol. 87, pp240-247), "limited success in animal models all too often leads directly to clinical trials" (page 245, middle column, paragraph 2, lines 1-3) and the quandary of human gene therapy is that "it sort of works" (page 246, right column, paragraph 3, lines 1-3). Thus, animal models are not truly reflective of success in humans and are thus, not predictive. This suggests that studies in mice and guinea pigs are not truly predictive of effects in other mammals and humans and it would require undue experimentation on the part of a skilled artisan to use the instant invention in any other mammal or individual.

Thus, due to the art recognized unpredictability of achieving therapeutic levels of expression following direct administration of nucleic acids, as explained herein above, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of the ISS sequence, the lack of guidance

concerning the reduction of the severity and/or recurrence of symptoms in mammals and animals other than mice and guinea pigs, and the breadth of the claims, it would have required undue experimentation to practice the instant invention and the skilled artisan would not have predicted success in reducing the severity and/or recurrence of a symptom of HSV-2 infections in any and all mammals and any and all individuals using the ISS of the instant case.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29-35 are indefinite in their recitation of "instructions for administration...". It is unclear what the instructions would say. Thus, the metes and bounds of the claims are not clearly set forth.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 29-32, 35 are rejected under 35 U.S.C. 102(a) as being anticipated by Krieg et al. (1999, Journal of gene medicine, vol. 1, pp. 56-63).

The applicant claims an article of manufacture comprising a composition comprising an immunostimulatory sequence and instructions for administration of said composition. Instructions as to the use of a product are not given patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963) (MPEP 2111.02). Further, mere printed matter cannot impart a patentable feature to a claim (In re Gulack 217 USPQ 401 (1983).

Krieg et al. (1999, Journal of gene medicine, vol. 1, pp. 56-63) teach the sequences AACGTTCC and GACGTTCC (see Table 1) as immunostimulatory sequences, which encompasses the limitations of claims 29-32, 35. Thus, by teaching all of the limitations of claims 29-32, 35, Krieg et al. clearly anticipates the instant invention.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10-14, 16-19, 20-24, 26-28, 29-33, 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwartz et al. (1998, PCT International Publication No. WO98/55495).

The applicant claims an article of manufacture comprising a composition comprising an immunostimulatory sequence and instructions for administration of said composition. Instructions as to the use of a product are not given patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963) (MPEP 2111.02). Further, mere printed matter cannot impart a patentable feature to a claim (In re Gulack 217 USPQ 401 (1983).

Schwartz et al. (1998) teach an ISS sequence for treating herpes. In particular, they teach ISS sequences of AACGTTCC, AACGTTCG, GACGTTCC, GACGTTCG (page 10, line 8) and SeqID. NO.1 (claim 5, page 29, Table 1, SeqID No.2) of the instant invention.

Thus, by teaching all of the limitations of claims 10-14, 16-19, 20-24, 26-28, 29-33, 35, Schwartz et al. clearly anticipates the instant invention.

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the

> treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 29-32, 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Krieg et al. (US patent No. 6218371).

The applicant claims an article of manufacture comprising a composition comprising an immunostimulatory sequence and instructions for administration of said composition. Instructions as to the use of a product are not given patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963) (MPEP 2111.02). Further, mere printed matter cannot impart a patentable feature to a claim (In re Gulack 217 USPQ 401 (1983).

Krieg et al. (US patent No. 6,218,371) teach the sequence AACGTTCG in their patent (see column 45, complement of sequence 11) as an immunostimulatory sequence, which encompasses the limitations of claims 29-32, 35. Thus, by teaching all of the limitations of claims 29-32, 35, Krieg et al. clearly anticipates the instant invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305 1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308 4242 for regular communications and (703) 308 4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-2982.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER

S. Pappu
April 5, 2002